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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,556	07/30/2001	Susanna M. Rybak	15280-3711US	9130

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EXAMINER	
GEBREYESUS, KAGNEW H	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,556	RYBAK ET AL.	
	Examiner	Art Unit	
	Kagnew H Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) *3,5 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4 and 6-14* is/are rejected.

7)☒ Claim(s) *4 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 3, 5, 15-21 have been cancelled. Claims 1,2,4,6-14 are amended, no new claims have been added.

Applicant's response dated April, 11, 2005 is acknowledged. The rejection under 35 U.S.C. 101 with respect to claims 1, 3, 5, 9-13, the rejection under 35 U.S.C. 112, second paragraph, of claims 1, 3, 5 and 8-14 have been dropped subsequent to the claim amendments.

However the rejection under 35 U.S.C. 112, first paragraph of claims 1, 3, 5-7, 9-14 the rejections of claims 1, 3, 5, 8-11 under 35 U.S.C. 102(b) as being anticipated by Sakakibara et al., (1992) as evidenced by Griffith et al., (1997) are maintained for the reasons provided in the previous office action and further stated below. The argument provided by applicants have not been found persuasive. In addition the rejection under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al. in view of Barker et al. have not been addressed by applicants therefore maintained.

Claim Rejections - 35 USC § 112

Claims 1, 2, 6, 7, 9-14 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1, 3, 5-7, 9-14 are rejected because the specification, while being enabling for an RNase polypeptide of SEQ ID NO: 2 and 4 does not reasonably provide enablement for any RNase polypeptide from any source having an N-terminus of SEQ ID NO: 9 selectively toxic to any source of proliferating endothelial cells. In addition within the group of RNase A are also included polypeptides of

plant origin example self-incompatibility from flowering plants which is not enabled by or supported by the specification.

Claims 1, 2, 6, 7, 9-14 are so broad as to encompass any RNase polypeptide with the only limitation of being cytotoxic to proliferating endothelial cells. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides encoding RNase A broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the enablement in the disclosure is limited to the nucleotide and encoded amino acid sequence of only SEQ ID NO: 2 and SEQ ID NO: 4.

The proteins of SEQ ID NO: 2 and SEQ ID NO: 4 have have been shown to have RNase activity as well as a cytotoxic activity. The specification does not provide a method by which one of ordinary skill in the art may obtain an RNase with a catalytic activity and cytotoxic activity selectively directed to endothelial cells by adding the amino acids $X^1X^2SLX^3V$ to any polypeptide belonging to RNase A superfamily polypeptides derived from any source including any animal or plant polypeptides.

The mammalian RNase A superfamily comprises a diverse array of ribonucleolytic proteins that have a variety of biochemical activities and physiological functions. Including the sequence of SEQ ID NO: 9 in any RNase A polypeptide with the expectation of retaining activity

and selective toxicity to proliferating endothelial cells is unpredictable. While orthologs of specific genes from different species may have equivalent functions and characteristics, different genes that may belong in a family of genes may have divergent functions or specificities. It is therefore not routine in the art to add the sequence of SEQ ID NO: 9 to any polypeptide belonging to an RNase A superfamily with an expectation of producing a polypeptide with enzymatic activity and selective cytotoxicity to proliferating endothelial cells and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any variation in the downstream sequence following the sequence of SEQ ID NO: 9 for a given protein to vary in terms of activity and selectivity e.g. self-incompatibility from flowering plants.

The specification does not support the broad scope of the claims which encompass any RNase polypeptide because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting RNase polypeptide activity since ; (B) the general tolerance of RNase polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any RNase A superfamily polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of RNase A having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art

is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claim 1, 2, 6, 8-11 rejected under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al., (1992) as evidenced by Griffith et al., (1997). Sakakibara et al., teach the isolation/purification of a unique RNase superfamily polypeptide, RNase UpI-2, from urine of pregnant women that include the additional N-terminal amino acid residues SLHV (serine, leucine, histidine and valine) in the coding sequence of the RNase superfamily polypeptide hEDN. Claims 1, 2, 6, 8-11 even with the present amendments encompass any RNase superfamily polypeptide with or without the glycine residue at position X^2. In the absence of the glycine residue the claimed RNase superfamily polypeptide will read on Sakakibara's sequence.

Claims 2, 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al. in view of Barker et al. Barker et al., teach the complete sequence of human EDN of which the protein of Sakakibara et al., is a processing variant (see page 148 of Sakakibara et al.) and compare the polypeptide sequence of EDN and ECP (eosinophile cationic protein) polypeptides and show the putative signal peptide cleavage site for both proteins. Sakakibara et al., teach an RNase polypeptide that include residues SLHV (serine, leucine, histidine and valine) that are

part of the signal sequence in the sequence disclosed by Barker et al. Including a methionine is routinely practiced for the purpose of recombinant production of proteins. The many advantages of recombinant production of useful proteins are well known within the art. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Therefore, it would have been obvious to one of ordinary skill in the art to include a methionine residue for the purposes of recombinant production of the polypeptide.

Applicants contend that the reference, Sakakibara et al., does not provide an RNase A that has an N-terminal sequence fitting the profile of SEQ ID NO: 9, however, they also define SEQ ID NO: 9 to be either MSLXV or MGSXV as the N-terminal portion that allegedly constitutes novelty. Applicant also recognizes SLXV as the N-terminal of the sequence disclosed by Sakakibara et al. it would therefore have been obvious for a person of ordinary skill in the art to include a methionine residue for the purpose of expressing the RNase polypeptide of Sakakibara et al.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakakibara et al., (1992) in view of Griffith et al., (1997). Sakakibara et al., teach the isolation/purification of a unique RNase superfamily polypeptide, RNase UpI-2, from urine of pregnant women that includes additional N-terminal amino acid residues in the coding sequence of the RNase superfamily polypeptide hEDN. In addition, functional characterization of the UpI-2 by it's catalytic activity, sensitivity to inhibition by divalent cations and its immunoreactivity with

antibodies to non-secretory RNase 1 indicates that RNase UpI-2 is a member of the RNase superfamily proteins. Furthermore, residues 1 to 4 and 5-20 of RNase UpI-2 show 100% identity to residues –4 to -1 of eosinophil-derived neurotoxin (EDN) and 1-16 of all the known non-secretory RNase (page 327 column 2). The cytotoxic effect of RNase UpI-2 on KS Y-1 cells is inherent to the protein as evidenced by Griffith et al., who isolated/purified the an RNase polypeptide from essentially the same source and demonstrated specific cytotoxic effects towards KS Y-1 cells. Griffith et al., did not test KS Y-3, KS 1, KS 2, KS 3, KS 4, KS 5 and KS 6 cells. However it would have been obvious for a person of ordinary skill in the art to examine the effects of the RNase on other Kaposi sarcoma cell lines to determine efficacy and/or specificity of cytotoxic activity.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30 am-5: 30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

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